# ANTI-HIV ANTIBODY 10-1074 VARIANTS

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 62/731,356, filed Sep. 14, 2018. The foregoing application is incorporated by reference herein in its entirety.

## STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

**[0002]** This invention was made with government support under Grant No. P01 AI081677 awarded the NIH. The government has certain rights in the invention.

## FIELD OF THE INVENTION

**[0003]** This invention relates generally to broad and potent antibodies against Human Immunodeficiency Virus ("HIV") and more specifically to anti-HIV antibody 10-1074 variants and the use thereof.

## BACKGROUND OF THE INVENTION

**[0004]** HIV causes acquired immunodeficiency syndrome (AIDS), a condition in humans characterized by clinical features including wasting syndromes, central nervous system degeneration and profound immunosuppression that results in life-threatening opportunistic infections and malignancies. Since its discovery in 1981, HIV type 1 (HIV-1) has led to the death of at least 25 million people worldwide. It is predicted that 20-60 million people will become infected over the next two decades even if there is a 2.5% annual decrease in HIV infections. There is a need for therapeutic agents and methods for treatment or inhibition of HIV infection.

**[0005]** Some HIV infected individuals show broadly neutralizing IgG antibodies in their serum. Yet, little is known regarding the specificity and activity of these antibodies, despite their potential importance in designing effective vaccines. In animal models, passive transfer of neutralizing antibodies can contribute to protection against virus challenge. Neutralizing antibody responses also can be developed in HIV-infected individuals, but the detailed composition of the serologic response is yet to be fully uncovered.

## SUMMARY OF INVENTION

**[0006]** The present disclosure relates to a new category of broadly-neutralizing anti-HIV antibodies, having modified light chain variable regions and/or heavy chain variable regions leading to improved biophysical characteristics, as well as methods of production and methods of use thereof.

**[0007]** Accordingly, in a first aspect, the present disclosure provides an isolated anti-HIV antibody, or antigen-binding portion thereof, including a light chain variable region having a light chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the light chain variable regions of SEQ ID NOs: 3-13, 22, 24-28, 35-39, 43-45, and 47. The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more light chain substitutions at one or more residues located within or outside the light chain variable region. The one or more residues are selected from the group consisting of LmdV:Y2, LmdV:R7, LmdV:P9, LmdV:E17, LmdV:H46, LmdV:P81.1, LmdV:I81.3, LmdV:N82, LmdV:R88, LmdV:D110, and LmdV:A142.

**[0008]** In another aspect, the present disclosure provides an isolated anti-HIV antibody, or antigen-binding portion thereof, including a heavy chain variable region having a heavy chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the heavy chain variable regions of SEQ ID NOs: 61-94. The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more heavy chain substitutions at one or more residues located within or outside of the heavy chain variable region. The one or more residues are selected from the group consisting of HV:D29, HV:S47, HV:N75, HV:V79, HV:R82, HV:L89, HV:T108, and HV:K141.

**[0009]** In another aspect, the present disclosure provides an isolated anti-HIV antibody, or antigen-binding portion thereof, including a light chain variable region having a light chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the light chain variable regions of SEQ ID NOs: 3-13, 22, 24-28, 35-39, 43-45, and 47. The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more light chain substitutions at one or more residues selected from the group consisting of LmdV:Y2, LmdV:R7, LmdV:P9, LmdV:E17, LmdV:H46, LmdV:P81.1, LmdV:I81.3, LmdV:N82, LmdV:R88, LmdV:D110, and LmdV:A142. The anti-HIV antibody, or antigen-binding portion thereof, further includes a heavy chain variable region having a heavy chain amino acid sequence is at least 75% identical to a polypeptide sequence selected from the group consisting of the heavy chain variable regions of SEQ ID NOs: 61-94. The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more heavy chain substitutions at one or more residues selected from the group consisting of HV:D29, HV:S47, HV:N75, HV:V79, HV:R82, HV:L89, HV:T108, and HV:K141.

**[0010]** In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof includes the one or more light chain substitutions selected from the group consisting of LmdV:Y2P, LmdV:R7P, LmdV:P9S, LmdV:E17Q, LmdV:H46Q, LmdV:P81.1N, LmdV:I81.3S, LmdV:N82G, LmdV:R88T, LmdV:D110E, and LmdV:A142G or conservative substitutions thereof (i.e., LmdV:P9C, LmdV:P9T, LmdV:E17N, LmdV:H46N, LmdV:P81.1Q, LmdV:R88C, LmdV:R88S).

**[0011]** In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof includes the one or more heavy chain substitutions selected from the group consisting of HV:D29G, HV:S47P, HV:N75Q, HV:V79T, HV:R82V, HV:L89F, HV:T108R, and HV:K141Q or conservative substitutions thereof (i.e., HV:L89W, HV:L89Y, HV:T108H, HV:T108K, HV:K141N).

**[0012]** In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof, includes the one or more light chain substitutions selected from the group consisting of LmdV:Y2P, LmdV:R7P, LmdV:P9S, LmdV:E17Q, LmdV:H46Q, LmdV:P81.1N, LmdV:I81.3S, LmdV:N82G, LmdV:R88T, LmdV:D110E, and LmdV:A142G or conservative substitutions thereof (i.e., LmdV:P9C, LmdV:P9T, LmdV:E17N, LmdV:H46N, LmdV:P81.1Q, LmdV:R88C, LmdV:R88S) and the one or more heavy chain substitutions selected from the group consisting of HV:D29G, HV:S47P, HV:N75Q, HV:V79T, HV:R82V,